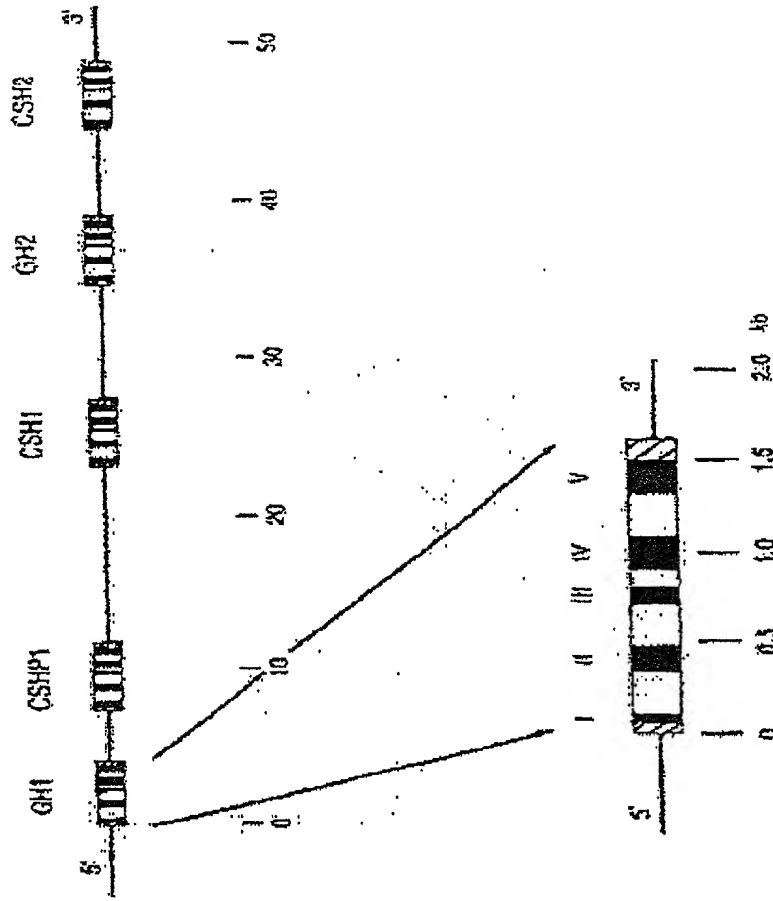


**Figure 1**



**Fig. 1 Human growth hormone gene cluster on chromosome 17q23. The fine structure of the GH1 gene is shown below. The scales are in kilobases (kb)**

Figure 2

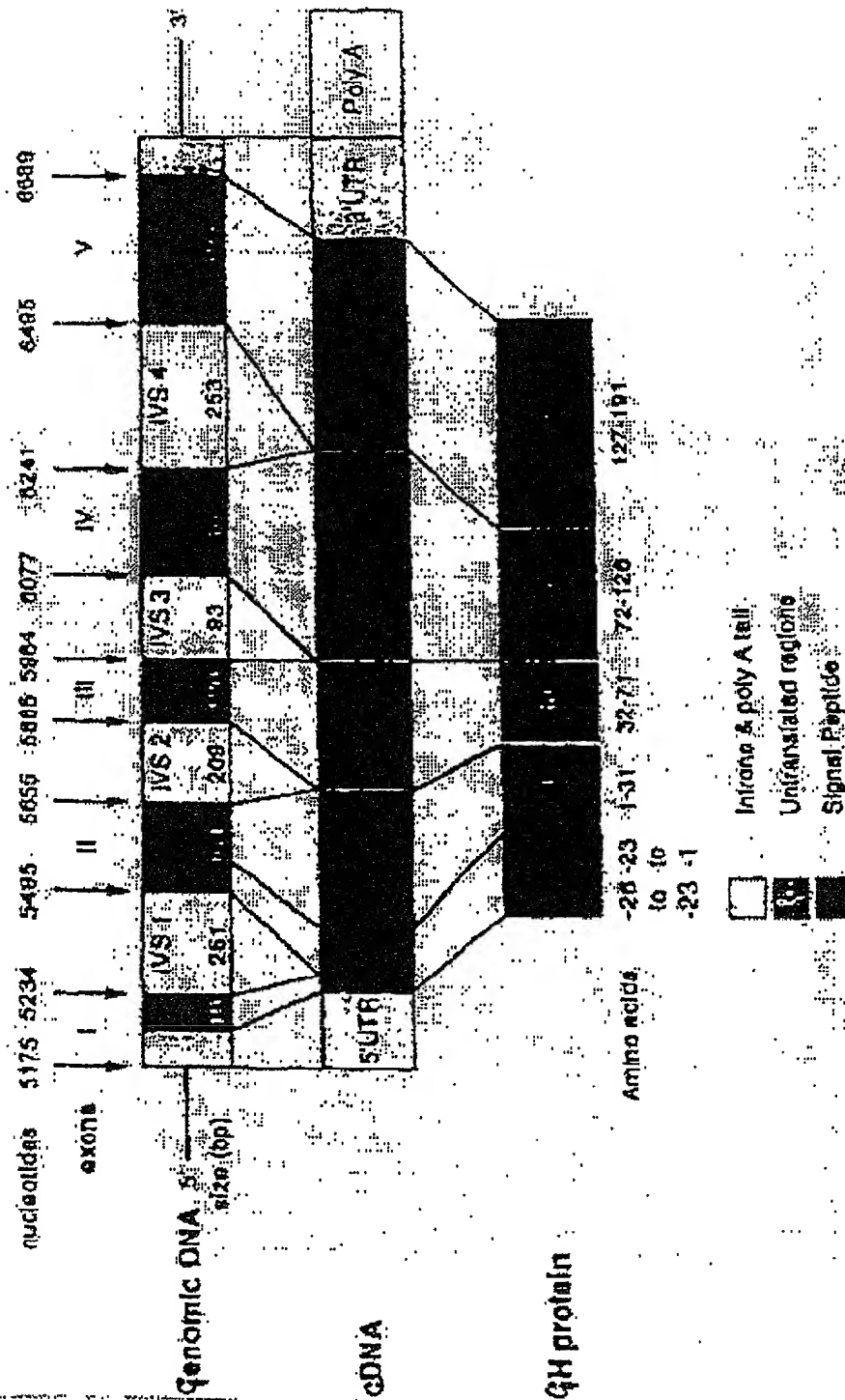
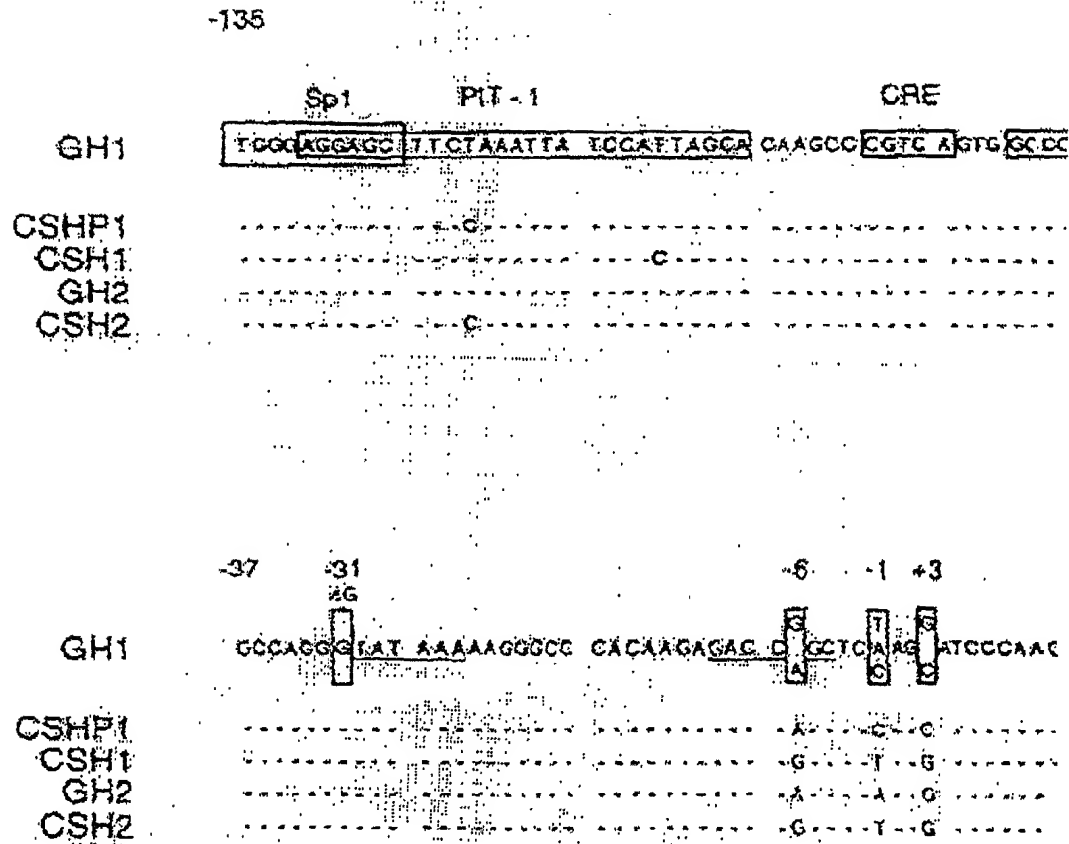


Figure 3



**Fig. 3.** Structure of the 5' untranslated region and promoter region of the human *GH1* gene. *Horizontal boxes* denote known, putative or inferred binding sites for transcription factors. *Vertical boxes* indicate polymorphic sites in the human population (data from Giordano et al. 1997; Wagner et al. 1997). The numbering scheme is by reference to the transcriptional initiation site at +1. The TATA box, a Chi-like element and the ATG translational initiation site are *underlined*. The human *GH1* promoter is also aligned with the promoters of the human *CSHP1*, *CSH1*, *GH2* and *CSH2* genes in order to indicate both the extent of homology but also the differences evident between promoters.



751-825  
aaaaaaaaagtgagaagcagctccactccaggaggaagacacacacatcccgtggacaaggatgcagatgt  
tttttttgcctcgtcgagggtgaggtccctccctctgtgtgtgtagggcacctgttccctacgtctaca

5  
ggcctttggccttcattcccatcgcgggcaggatctgttttcaggaggggaggagcgcggggcccca  
ccggaaacccgaagtaaggtaagtcggcccgccctagacaaaagtcctccccgcctccgtcgccccggggt

10  
ccgcctgcagggttatttgcacattttgagccgtgctgttcctcactggtgacaacagccctgagccccattt  
ggcggacgtccaataaacagtgtaaaactcggcacgacaaggagtgaccactgttgtcgggactcggggtaaa  
tgggctcatgatgcccttttctccagaacaggagggcctcacaaagcctacccctgcctctgcctcggctgccc  
accgagtaactacgggaaaagaagggtcttgcctccggagtgttcggatggggaaggagcgggagccgagcggg

15  
ggggcttcacattctgacttctgacgacacccctcccttccagggaaggcaacatcaaaaataaggaaatgggggccag  
ccccgaagtgaagactgaagactgctgtggagggaaggtccctccgttgtagtatttcttaccctccggctc

20  
ggtcggggcgaagggaacaggggctcagggggtggggaagcaagaaggcagccccagccaccctaggatgcc  
ccagcccgcttccctgttccccgagtcccccaccctctcgttcttccgtcgtgggggtcgggtgggatcctacgg  
gggagggggaagaaacctcagggaagaagagctcagacccctgcctccttctccagccccagggtgtcctggatctg  
ccctcccccttcttgagtccttcttcttctcagagtctgggacgggaggaagaggtcgggtccacaggaacctagac

25  
ctgggctgctgtgactgggaaaagacctgctaagaaggacgtgggtttgagtcctgacccagcagtgtagcagcc  
gaccgcgacgacactgaccttttcttgacgattcttctgcacccaaactcaggactgggtcgtcacatcgtcgg  
aggaaacctccccagggtaccagtggttctctactaagggtggctctgccccaaacggaggagcgtctgcacatg  
tcctttggagggtccaatggtcaccagaagatgattcccaccgagacgggggttgctccctccgcagacgtgtac

30  
catcaggggcaatcgcgctggtctcaatgacccggtgggtgcctggggcggaaggcattggctgggcaagcagag  
gtagtcgcgttagcgcgaccagagttactggccacccacggacccccgcctccccgtaacccgaccgtttcgtctc

5 ttcctgccccacatgccaacagaccccatgaggcaacacccattcttaacctctcagtgaccaagggttcctcat 1501-1575  
 aagggacgggtgtacggtgtcgtgggtactccgttggtggtagaattggagagtcactggttccaaggagta  
 10 tttcgtaaaatagaaaataagcccaatagcgcgtttttttgtgtgttttctgggggtttttctgagacaagatct 1576-1650  
 aaagcattttatctttatcgggttatcgcgcaaaaaaacacaacaaagaccccccaaaagactctgttctaga  
 15 tgctctgtgtccaggctggagtgagtgagtggtgcaatctccattcacgggcaacctctgccacctggactcaagtga 1651-1725  
 acgagacaacaggtccgacctcacgtcaccacgttagaggttaagtgcggttgagagcgtggacctgagttcact  
 20 ttcacccacctcagcctccgagtagctgggactacaggtcatgctactacacctggtaaatctgtgtatttctt 1726-1800  
 aagtggtggagtcggaggctcatgacctgatgtccagtagcatgatgtggaccgattagacacataaagaa  
 25 gtagagacaggttttactatgttgcccaggctggtctcaaaactcctgagctcaagcgatccacccgcctcagcct 1801-1875  
 catctctgtccaaaatgatacaacgggtccgaccagagtttgaggactcgagttcgtaggtggcgagtcgga  
 30 cccaaagtgtgggattacaggcgtgagccactgcgcccggcccccacacagtcggttggaaggcgagctgtgc 1876-1950  
 gggtttcacgacctaatgtccgactcggtagcgcgggcggtgtgtcacgcaaccagcttcccgtcgacacg  
 35 acattgaaggccatcctgcattctgaggtagcttggtgaatgtggtggacggcacgccctgaggaggcgaggagtg 1951-2025  
 tgtaacttcggtaggacgtagactccatgaaccacttacaccacctgccgtgcgggactcctcccgctcctcac  
 2026-2030  
 cgagg  
 gctcc

25 PCR primers are marked in bold (42-1984 = 1942bp).  
 Sequencing primers are underlined (GHLCR3.1, 541-558; GHLCR3.2, 1006-1023; GHLCR3.3, 1422-1440;  
 GHLCR5.0, 640-658)

Figure 5

	-700	ctgtttcttg	gtttgtgtct	ctgctgcaag	tccaaggagc	tggggcaata	-651
5	-650	ccttgagtct	gggttcttcg	tccccaggga	cctgggggag	ccccagcaat	-601
	-600	gctcagggaa	aggggagagc	aaagtgtggg	gttgggttctc	tctagtggtc	-551
	-550	agtgttggaa	ctgcatccag	ctgactcagg	ctgacccagg	agtcctcagc	-501
	-500	agaagtggaa	ttcaggactg	aatcgtgctc	acaaccccc	caatctattg	-451
	-450	gctgtgcttg	gccccctttc	ccaacacaca	cattctgtct	ggtgggtgga	-401
10	-400	ggttaaaca	gccccggagg	ggaaagggat	aggatagaga	atgggatgtg	-351
	-350	gtcggtaggg	gggtctcaagg	actggctatc	ctgacatcct	tctccgcgtt	-301
	-300	caggttggcc	accatggcct	gccccagag	ggcaccacag	tgacccttaa	-251
	-250	agagaggaca	agttgggtgg	tatctctggc	tgacactctg	tgacaaccc	-201
	-200	tcacaacact	ggtagcgggt	gggaaggaaa	gatgacaagc	cagggggcat	-151
15	-150	gatcccagca	tgtgtggggag	gagcttctaa	attatccatt	agcacaagcc	-101
	-100	cgtcagtgcc	cccatgcata	aatgtacaca	gaaacagggt	gggggagacag	-51
	-50	tgggagagaa	ggggccaggg	tataaaaagg	gcccacaaga	gaccagctca	-1
	+1	aggatcccaa	ggcccaactc	ccgaaccac	tcagggtcct	gtggacagct	+50
	+51	cacctagcgg	caATGGCTAC	AGgtaagcgc	ccctaaaatc	cctttgggca	+100
20	+101	caatgtgtcc	tgaggggaga	ggcagcgacc	tgtagatggg	acgggggcac	+150
	+151	taaccctcag	gttttggggct	tctgaatgtg	agtatcgcca	tgtaagccca	+200
	+201	gtatttggcc	aatctcagaa	agctcctggg	ccctggaggg	atggagagag	+250
	+251	aaaaacaac	agctcctgga	gcaggagag	tgctggcctc	ttgctctccg	+300
	+301	gctccctctg	ttgcccctctg	gtttctcccc	agGCTCCCGG	ACGTCCCTGC	+350
25	+351	TCCTGGCTTT	TGGCCTGCTC	TGCCTGCCCT	GGCTTCAAGA	GGGCAGTGCC	+400
	+401	TTCCCAACCA	TTCCCTTATC	CAGGCTTTTT	GACAACGCTA	TGCTCCGCGC	+450
	+451	CCATCGTCTG	CACCAGCTGG	CCTTTGACAC	CTACCAGGAG	TTTgtaagct	+500
	+501	cttggggaat	gggtgcgcac	caggggtggc	aggaaggggg	gactttcccc	+550
	+551	cgtggggaat	taagaggagg	agactaagga	gctcagggtt	tttcccggaag	+600
30	+601	cgaaaatgca	ggcagatgag	cacacgctga	gtgaggttcc	cagaaaagta	+650
	+651	acaatgggag	ctgggtctcca	gcgtagacct	tggtggggcg	tccttctcct	+700
	+701	agGAAGAAGC	CTATATCCCA	AAGGAACAGA	AGTATTCAAT	CCTGCAGAAC	+750
	+751	CCCCAGACCT	CCCTCTGTTT	CTCAGAGTCT	ATCCGACAC	CCTCAACAG	+800
	+801	GGAGGAAACA	CAACAGAAAT	CCgtgagtg	atgccttctc	cccaggcggg	+850
35	+851	gatgggggag	acctgtagtc	agagccccc	ggcagcacag	ccaatgccc	+900
	+901	tccttccctc	gcagAACCTA	GAGCTGCTCC	GCATCTCCCT	GCTGCTCATC	+950
	+951	CAGTCGTGGC	TGGAGCCCCG	GCAGTTCCTC	AGGAGTGTCT	TCGCCAACAG	+1000
	+1001	CCTGGGTGTAC	GGCGCCTCTG	ACAGCAACGT	CTATGACCTC	CTAAAGGACC	+1050
	+1051	TAGAGGAAGG	CATCCAAACG	CTGATGGGGg	tgaggggtgg	gccaggggtc	+1100
40	+1101	cccaatcctg	gagccccact	gactttgaga	gctgtgttag	agaaacactg	+1150
	+1151	ctgcccctct	tttagcagtc	aggccctgac	ccaagagaac	tcaccttatt	+1200
	+1201	cttcatttcc	cctcgtgaat	cctccaggcc	tttctctaca	ccctgaaggg	+1250
	+1251	gagggaggaa	aatgaatgaa	tgagaaagg	agggaaacag	acccaagcgc	+1300
	+1301	ttggcctctc	cttctcttcc	ttcaactttg	agAGGCTGGA	AGATGGCAGC	+1350
45	+1351	CCCCGACTG	GGCAGATCTT	CAAGCAGACC	TACAGCAAGT	TCGACACAAA	+1400
	+1401	CTCACACAAC	GATGACGCAC	TACTCAAGAA	CTACGGGCTG	CTCTACTGCT	+1450
	+1451	TCAGGAAGGA	CATGGACAAG	GTCGAGACAT	TCCTGCGCAT	CGTGCACTGC	+1500
	+1501	CGCTCTGTGG	AGGGCAGCTG	TGGCTTCTAG	ctgcccgggt	ggcatccctg	+1550
	+1551	tgacccctcc	ccagtgcctc	tcctggccct	ggaagtgtgc	actccagtgc	+1600
50	+1601	ccaccagcct	tgtcct <u>aata</u>	aaattaagtt	gcatcatttt	gtctgactag	+1650
	+1651	gtgtccttct	ataatattat	ggggtggagg	ggggtggtat	ggagcaaggg	+1700
	+1701	gcaagttagg	aagacaacct	gtagggcctg	cggggtctat	tcgggaacca	+1750
	+1751	agctggagtg	cagtggcaca	atcttggtc	actgcaatct	ccgcctcctg	+1800
	+1801	ggttcaagcg	attctcctgc	ctcagcctcc	cgagttgttg	ggattccagg	+1850
55	+1851	catgcatgac	caggctcagc	taatttttgt	ttttttggta	gagacggggg	+1900
	+1901	ttcaccatat	tggccaggct	gggtctccaac	tcctaatactc	aggtgatcta	+1950
	+1951	cccaccttgg	cctcccaaat	tgctgggatt	acaggcgtga	accactgtc	+2000
	+2001	ccttccctgt	ccttctgatt	ttaaaataac	tataccagca	ggaggacgtc	+2050
	+2051	cagacacagc	ataggctacc	tgccatgccc	aaccgggtgg	acatttgagt	+2100
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	+2151	tgttgaattc	ctgggcctag	ggctgtgcca	gctgcctcgt	cccgtcacct	+2200
	+2201	tctggcttct	tctctccctc	catatcttag	ctgttttctc	catgagaatg	+2250
	+2251	ttccaaattc	gaaattttcta	tttaaccatt	atatattttac	ttgtttgcta	+2300

5	+2301	ttatctctgc	cccagtaga	ttgttagctc	cagaagagaa	aggatcatgt	+2350
	+2351	cttttgctta	tctagatatg	cccatctgcc	tggtacaatc	tctggcacat	+2400
	+2401	gttacaggca	acaactactt	gtggaattgg	tgaatgcatg	aatagaagaa	+2450
	+2451	tgagtgaatg	aatgaataga	caaaaggcag	aaatccagcc	tcaaagaact	+2500
10	+2501	tcagctctgg	taagaggaat	aaaatgtctg	caaataggcca	caggcacagg	+2550
	+2551	caaaggaagg	aggggctatt	tccagctgag	ggcaccccat	caggaaagca	+2600
	+2601	cccagacttt	cctacaacta	ctagacacat	ctcgatgctt	ttcacttttc	+2650
	+2651	tatcaatgga	tctgttccct	ggagataaat	ccccaaagtg	aaattactta	+2700
15	+2701	gcacgtccag	ttaggttagt	ccttgtgtac	ttcttggttg	ttcagagatc	+2750
	+2751	atcaaccagt	gcaaacaaatc	cccccatcaa	tacacagtag	tgccctgccc	+2800
	+2801	tctccccccg	aggtcttccg	aggcccttcc	tccgtgcctg	aacccctcgg	+2850
	+2851	acatatcata	tggcaaaactg	aagtgtccaa	cgagatatag	gaagtgaaac	+2900
	+2901	acgatgtaca	ctgaacactg	caatacaaat	atgcagcatg	aagtgcctcg	+2950
	+2951	gttcactaac	ccgagctacg	ctgggtgcctt	cttttctacc	actttcctta	+3000

[illegible]



**Figure 6**

Growth hormone 1  
 5 Gene symbol : *GHI*  
 Location : 17q

1 2  
 -26 ATG GCT ACA G↓GC TCC CGG ACG TCC CTG CTC CTG GCT TTT GGC CTG -12  
 Met Ala Thr G ly Ser Arg Thr Ser Leu Leu Leu Ala Phe Gly Leu

10 -11 CTC TGC CTG CCC TGG CTT CAA GAG GGC AGT GCC TTC CCA ACC ATT 4  
 Leu Cys Leu Pro Trp Leu Gln Glu Gly Ser Ala Phe Pro Thr Ile

15 5 CCC TTA TCC AGG CTT TTT GAC AAC GCT AGT CTC CGC GCC CAT CGT 19  
 Pro Leu Ser Arg Leu Phe Asp Asn Ala Ser Leu Arg Ala His Arg

20 2 3  
 20 CTG CAC CAG CTG GCC TTT GAC ACC TAC CAG GAG TTT↓GAA GAA GCC 34  
 Leu His Gln Leu Ala Phe Asp Thr Tyr Gln Glu Phe Glu Glu Ala

20 35 TAT ATC CCA AAG GAA CAG AAG TAT TCA TTC CTG CAG AAC CCC CAG 49  
 Tyr Ile Pro Lys Glu Gln Lys Tyr Ser Phe Leu Gln Asn Pro Gln

25 50 ACC TCC CTC TGT TTC TCA GAG TCT ATT CCG ACA CCC TCC AAC AGG 64  
 Thr Ser Leu Cys Phe Ser Glu Ser Ile Pro Thr Pro Ser Asn Arg

3 4  
 65 GAG GAA ACA CAA CAG AAA TCC↓AAC CTA GAG CTG CTC CGC ATC TCC 79  
 Glu Glu Thr Gln Gln Lys Ser Asn Leu Glu Leu Leu Arg Ile Ser

30 80 CTG CTG CTC ATC CAG TCG TGG CTG GAG CCC GTG CAG TTC CTC AGG 94  
 Leu Leu Leu Ile Gln Ser Trp Leu Glu Pro Val Gln Phe Leu Arg

95 AGT GTC TTC GCC AAC AGC CTG GTG TAC GGC GCC TCT GAC AGC AAC 109  
 Ser Val Phe Ala Asn Ser Leu Val Tyr Gly Ala Ser Asp Ser Asn

35 110 GTC TAT GAC CTC CTA AAG GAC CTA GAG GAA GGC ATC CAA ACG CTG 124  
 Val Tyr Asp Leu Leu Lys Asp Leu Glu Glu Gly Ile Gln Thr Leu

4 5  
 125 ATG GGG↓AGG CTG GAA GAT GGC AGC CCC CGG ACT GGG CAG ATC TTC 139  
 Met Gly Arg Leu Glu Asp Gly Ser Pro Arg Thr Gly Gln Ile Phe

40 140 AAG CAG ACC TAC AGC AAG TTC GAC ACA AAC TCA CAC AAC GAT GAC 154  
 Lys Gln Thr Tyr Ser Lys Phe Asp Thr Asn Ser His Asn Asp Asp

45 155 GCA CTA CTC AAG AAC TAC GGG CTG CTC TAC TGC TTC AGG AAG GAC 169  
 Ala Leu Leu Lys Asn Tyr Gly Leu Leu Tyr Cys Phe Arg Lys Asp

170 ATG GAC AAG GTC GAG ACA TTC CTG CGC ATC GTG CAG TGC CGC TCT 184  
 Met Asp Lys Val Glu Thr Phe Leu Arg Ile Val Gln Cys Arg Ser—

50 185 GTG GAG GGC AGC TGT GGC TTC TAG  
 Val Glu Gly Ser Cys Gly Phe \*

**Figure 7**

GH variant *Glu-Gly30*  
 Location : 17q

1 2

-26 ATG GCT ACA G↓GC TCC CGG ACG TCC CTG CTC CTG GCT TTT GGC CTG -12  
 Met Ala Thr G ly Ser Arg Thr Ser Leu Leu Leu Ala Phe Gly Leu

10 -11 CTC TGC CTG CCC TGG CTT CAA GAG GGC AGT GCC TTC CCA ACC ATT 4  
 Leu Cys Leu Pro Trp Leu Gln Glu Gly Ser Ala Phe Pro Thr Ile

5 CCC TTA TCC AGG CTT TTT GAC AAC GCT AGT CTC CGC GCC CAT CGT 19  
 Pro Leu Ser Arg Leu Phe Asp Asn Ala Ser Leu Arg Ala His Arg

15 20 CTG CAC CAG CTG GCC TTT GAC ACC TAC CAG GAG TTT↓GGG GAA GCC 34  
 Leu His Gln Leu Ala Phe Asp Thr Tyr Gln Glu Phe Gly Glu Ala

35 TAT ATC CCA AAG GAA CAG AAG TAT TCA TTC CTG CAG AAC CCC CAG 49  
 Tyr Ile Pro Lys Glu Gln Lys Tyr Ser Phe Leu Gln Asn Pro Gln

20 50 ACC TCC CTC TGT TTC TCA GAG TCT ATT CCG ACA CCC TCC AAC AGG 64  
 Thr Ser Leu Cys Phe Ser Glu Ser Ile Pro Thr Pro Ser Asn Arg

25 65 GAG GAA ACA CAA CAG AAA TCC↓AAC CTA GAG CTG CTC CGC ATC TCC 79  
 Glu Glu Thr Gln Gln Lys Ser Asn Leu Glu Leu Leu Arg Ile Ser

80 CTG CTG CTC ATC CAG TCG TGG CTG GAG CCC GTG CAG TTC CTC AGG 94  
 Leu Leu Leu Ile Gln Ser Trp Leu Glu Pro Val Gln Phe Leu Arg

30 95 AGT GTC TTC GCC AAC AGC CTG GTG TAC GGC GCC TCT GAC AGC AAC 109  
 Ser Val Phe Ala Asn Ser Leu Val Tyr Gly Ala Ser Asp Ser Asn

110 GTC TAT GAC CTC CTA AAG GAC CTA GAG GAA GGC ATC CAA ACG CTG 124  
 Val Tyr Asp Leu Leu Lys Asp Leu Glu Glu Gly Ile Gln Thr Leu

35 125 ATG GGG↓AGG CTG GAA GAT GGC AGC CCC CGG ACT GGG CAG ATC TTC 139  
 Met Gly Arg Leu Glu Asp Gly Ser Pro Arg Thr Gly Gln Ile Phe

40 140 AAG CAG ACC TAC AGC AAG TTC GAC ACA AAC TCA CAC AAC GAT GAC 154  
 Lys Gln Thr Tyr Ser Lys Phe Asp Thr Asn Ser His Asn Asp Asp

155 GCA CTA CTC AAG AAC TAC GGG CTG CTC TAC TGC TTC AGG AAG GAC 169  
 Ala Leu Leu Lys Asn Tyr Gly Leu Leu Tyr Cys Phe Arg Lys Asp

45 170 ATG GAC AAG GTC GAG ACA TTC CTG CGC ATC GTG CAG TGC CGC TCT 184  
 Met Asp Lys Val Glu Thr Phe Leu Arg Ile Val Gln Cys Arg Ser

185 GTG GAG GGC AGC TGT GGC TTC TAG  
 Val Glu Gly Ser Cys Gly Phe \*

Figure 8

WT-HIS vs VAR 14

